CURRENT THERAPEUTIC RESEARCH
VOLUME 70, NUMBER 5, OCTOBER 2009

Brief Report

Effectiveness and Tolerability of Rosiglitazone on Insulin Resistance and Body Composition in Nondiabetic Thai Patients Undergoing Continuous Ambulatory Peritoneal Dialysis: A 12-Week Pilot Study

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ABSTRACT

BACKGROUND: Patients with chronic renal insufficiency, especially those undergoing continuous ambulatory peritoneal dialysis (CAPD), normally have insulin resistance due to deficiencies in insulin secretion and degradation, as well as tissue resistance to insulin at both receptor and postreceptor levels.

OBJECTIVE: The aim of this study was to investigate the effectiveness and tolerability of rosiglitazone on insulin resistance and body composition in patients without diabetes mellitus (DM) undergoing CAPD.

METHODS: This pilot study included a pretest and posttest with a repeated-measure design in a small number of patients. CAPD patients without DM received rosiglitazone 2-mg tablets BID for 12 weeks. Homeostasis Model Assessment Index of Insulin Resistance (HOMA-IR) and bioelectrical impedance analysis (BIA) were used to assess insulin resistance and body composition, respectively. Tolerability was assessed using laboratory analyses as well as physical examination findings to evaluate peripheral edema. Peripheral edema was assessed by the study investigators.

RESULTS: Thirteen Thai patients (mean [SD] age, 54.17 [11.42] years [range, 35–85 years]; body mass index [BMI], >20 to <30 kg/m^2; fasting blood glucose [FBG] concentration, <5.39 mmol/L) were included in the study. One patient was withdrawn due to illness unrelated to the study. No significant difference was found in FBG concentration between baseline and posttreatment (after 12 weeks of treatment) (5.45 [0.59] vs 5.24 [0.51] mmol/L), but fasting plasma insulin concentrations (28.50 [23.70] vs 10.15 [4.22] μIU/mL; P = 0.005) and HOMA-IR score (6.70 [5.23] vs 2.40 [1.15]; P = 0.011) were significantly lower. There were no significant changes in weight or BMI from baseline to posttreatment. Seven subjects (58.3%)

Accepted for publication June 8, 2009.
doi:10.1016/j.curtheres.2009.10.002

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experienced weight gain at week 4, while 2 patients (16.7%) still had weight gain after 12 weeks of treatment. A significant increase was found between baseline and posttreatment in total body water (38.03 [4.55] vs 42.44 [5.99] L; $P = 0.018$), extracellular fluid (20.24 [3.75] vs 26.22 [8.69] L; $P = 0.005$), plasma fluid (4.29 [0.80] vs 5.20 [0.93] L; $P = 0.005$), and interstitial fluid (14.99 [2.78] vs 17.68 [3.07] L; $P = 0.040$). Using BIA, no significant changes were observed in intracellular fluid, fat mass, or liver function. After 12 weeks of rosiglitazone administration, 2 patients (16.7%) had mild edema.

CONCLUSIONS: Rosiglitazone 2 mg BID for 12 weeks was associated with significantly improved insulin resistance in this small group of nondiabetic Thai patients undergoing CAPD. There was a significant increase in total body water and extracellular fluid after administration of rosiglitazone for 12 weeks. There were no significant changes in FBG, weight, or BMI. (*Curr Ther Res Clin Exp.* 2009;70:377–389) © 2009 Excerpta Medica Inc.

KEY WORDS: rosiglitazone, insulin resistance, body composition, nondiabetic, CAPD.

INTRODUCTION

Metabolic syndrome represents a cluster of disturbances that are risk factors for cardiovascular disease, including type 2 diabetes mellitus (DM), abdominal obesity, hypertension, and dyslipidemia.[1] Studies have found an association between insulin resistance or compensatory hyperinsulinemia and kidney disease[2] or atherosclerotic cardiovascular disease.[3] Patients with chronic renal insufficiency, especially those undergoing continuous ambulatory peritoneal dialysis (CAPD), normally have insulin resistance due to deficiencies in insulin secretion and degradation, as well as tissue resistance to insulin at both receptor and postreceptor levels.[4] Moreover, the dialysis solutions used in CAPD cause an additional glucose load of 100 to 300 g/d, resulting in tissue resistance to insulin.[5]

Rosiglitazone, a member of the thiazolidinedione drug class, is an antidiabetic agent that is a modulator of the peroxisome proliferator-activated receptor (PPAR). The drug improves insulin resistance in patients with type 2 DM by increasing insulin sensitivity in the liver, adipose tissue, and muscle.[6,7] This, in turn, leads to improvement in insulin-mediated glucose disposal and hence to a decrease in insulin requirement.[8] Since thiazolidinediones can be used effectively in reducing blood glucose concentration and insulin resistance in diabetic patients with chronic kidney diseases, it is worth determining whether the same effects will be found in nondiabetic patients with renal impairment. However, there is a growing recognition that edema can occur in patients treated with either rosiglitazone or pioglitazone.[9–11] People with type 2 DM are at increased risk for cardiovascular diseases; therefore, the edema that sometimes accompanies the use of a thiazolidinedione is a concern because it might indicate congestive heart failure.[12,13] Hong et al[14] found that PPAR-γ activation may enhance sodium reabsorption in the cortical collecting ducts via regulation of the epithelial sodium channel (ENaC), resulting in peripheral edema. Human

ENaC is expressed in the distal portion of the renal tubule and is regulated by aldosterone and vasopressin. The channel plays an important role in the regulation of sodium balance, blood volume, and blood pressure by sodium reabsorption.[15] In patients with renal deficiency, ENaCs do not function properly, resulting in reduced sodium reabsorption. Because of this, we hypothesized that the peripheral edema caused by thiazolidinedione administration should not occur in patients with end-stage renal disease.

In addition to its effect on edema that may relate to weight gain, rosiglitazone also has a demonstrable effect on metabolic factors. It has been reported that thiazolidinediones redistribute adipose tissue from visceral fat mass to peripheral (subcutaneous) tissue, resulting in weight gain.[16–18] Apart from those mechanisms, weight gain after thiazolidinedione administration may result from increased eating, since blood glucose concentration can be well controlled with thiazolidinediones and patients may experience increased appetite.[19]

This study was designed to investigate the effectiveness and tolerability of rosiglitazone on insulin resistance and body composition in nondiabetic patients undergoing CAPD. The effectiveness of rosiglitazone in reducing insulin resistance was assessed using the Homeostasis Model Assessment Index of Insulin Resistance (HOMA-IR). We studied the tolerability of rosiglitazone in CAPD by monitoring changes in body composition assessed by bioelectrical impedance analysis (BIA) and changes in lipid profiles and other laboratory data in conjunction with peripheral edema.

PATIENTS AND METHODS

Patients

Patients aged ≥18 years undergoing CAPD without DM (either type 1 or 2) who came for a physician appointment at Phramongkutklao Hospital (Bangkok, Thailand) between February and July 2008 were recruited into the study. Patients were eligible for the study if, for ≥90 days before enrollment, both their fasting blood glucose [FBG] concentration was <5.5 mmol/L and they had not taken a thiazolidinedione. They had to have been undergoing CAPD, have normal liver function, and be free of peritonitis for ≥3 months before entering the study. Additional inclusion criteria were an absence of residual renal function and no peritoneal failure.

Patients were excluded from the study if they had any acute illness, abnormal liver function tests, chronic liver disease, chronic infection (eg, tuberculosis or HIV), malignancy, autoimmune disease, lupus nephritis, cardiovascular disease (eg, ischemic heart disease or congestive heart failure), or recent gastrointestinal hemorrhage. In addition, patients who had received any medications that could potentially result in insulin resistance (eg, β-blockers, corticosteroids, verapamil, diltiazem, phenytoin, thyroid hormone, risperdal, haloperidol, and fibrate) within the past 3 months were excluded.

CAPD patients without DM who had a single pool Kt/V >1.2 (where K is the dialyzer clearance of urea, t is the dialysis time, and V is the patient's total body water) were enrolled. All patients routinely had 2-L 1.5% dialysate changes 4 times a day.

Written informed consent was obtained from all study participants after a thorough discussion of the protocol, its rationale, and potential risks. The protocol was

approved by the Ethics Committee of the Institutional Review Board of Phramongkutklao Hospital.

METHODS

The study was conducted at Phramongkutklao Hospital. Eligible patients were enrolled in a 12-week pretest and posttest study with a repeated-measure design. The patients were required to visit the hospital at 4, 8, and 12 weeks after enrollment. Throughout the study, patients were instructed to follow a weight-maintenance diet and they consulted with a dietician at each visit. The patients were instructed to continue their regular medications (antihypertensive drugs, erythropoietin, and lipid-lowering drugs) throughout the study.

Patients were administered rosiglitazone maleate 2 mg* BID for 12 weeks. Adherence was monitored by pill count at each visit. All measurements (eg, insulin resistance, body composition, edema, lipid profiles) were performed at 0 (baseline), 4, 8, and 12 weeks.

Assessment of Insulin Resistance

Insulin resistance was assessed using the HOMA-IR, originally described by Matthews et al,[20] in which HOMA-IR (mmol/L × μIU/mL) = fasting glucose (mmol/L) × fasting insulin (μIU/mL)/22.5. The HOMA-IR score correlates closely with the insulin sensitivity index measured using the gold standard—the euglycemic hyperinsulinemic clamp.[21,22] The index can be applied to patients with renal failure.[23]

Bioelectrical Impedance Analysis Measurement of Body Composition

Changes in body composition (water and fat composition) associated with rosiglitazone therapy were assessed using BIA (Bioscan 916, Maltron International Ltd., Essex, United Kingdom). Weight was measured after the dialysate solution was completely removed from the patient.

Blood Sampling and Assays

Before starting a dialysis session, blood was drawn in the morning after an overnight fast of ≥12 hours. Whole blood, which was used to measure hematocrit and hemoglobin concentration, was analyzed within 2 hours after it was drawn. EDTA-plasma was used to measure glucose, insulin, and lipid concentrations. Samples in EDTA-containing tubes were centrifuged immediately and the plasma was stored at –20°C until assayed. Serum was used for other biochemical assays (eg, hepatic enzyme activities). Freshly drawn blood was centrifuged immediately and the serum was stored at –20°C until analyzed.

Physical Examination

Peripheral edema was assessed by physical examination by the 3 study investigators (O.S., P.B., and P.A.). The degree of edema was scored visually as: +1 (very mild,

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<10%); +2 (mild, ≥10% to <25%); +3 (moderate, ≥25% to <50%); and +4 (severe, ≥50%).[24] For very mild edema (<10%), skin showed deeper furrowing than normal; and increasing edema grades resulted in a decrease of furrows. At severe edema stage (≥50%), no skin furrow was found. To minimize the bias from personal evaluation, body composition using BIA was measured at the time the physical examination was conducted.

Statistical Analysis

The objectives of the study were to assess the effect of rosiglitazone on insulin resistance and body composition. Based on the findings of a previous study,[25] the difference in the mean HOMA-IR score in the patients at baseline and after 12 weeks of treatment was 1.1, with 5% significance and 80% power; therefore, a sample size of 12 patients was considered sufficient. Statistical analysis was performed using SPSS version 10.0 (SPSS Inc., Chicago, Illinois). Results were expressed as mean (SD). Subset post hoc analyses were performed for FBG and fasting plasma insulin concentrations and HOMA-IR score to compare the differences between baseline and weeks 4, 8, and 12 of treatment. Corrections for multiple comparisons were not done. The statistical significance of the subset post hoc analysis was assessed using the Friedman test. A within-patient comparison of multiple analyses of water content in patients (eg, total body water, extracellular fluid, plasma fluid, interstitial fluid) between baseline and posttreatment (week 12) was analyzed using the Wilcoxon signed rank test. All statistical tests for differences were 2-tailed with $\alpha = 0.05$. $P < 0.05$ was considered statistically significant.

RESULTS

PATIENTS

Of the 38 patients with CAPD treated between February and July 2008, a total of 25 potential participants were excluded because they did not meet the inclusion criteria. Thirteen patients (mean [SD] age, 54.17 [11.42] years [range, 35–85 years]; body mass index (BMI), >20 to <30 kg/m^2; FBG concentration, <5.39 mmol/L) were included in the study. One patient was withdrawn at week 12 due to illness unrelated to the study.

INSULIN RESISTANCE BY HOMA-IR

The patients receiving CAPD therapy had no significant difference in FBG concentration between baseline and posttreatment (5.45 [0.59] vs 5.24 [0.51] mmol/L), but they did have significantly lower fasting plasma insulin concentrations (28.50 [23.70] vs 10.15 [4.22] μIU/mL; $P = 0.01$) and HOMA-IR scores (6.70 [5.23] vs 2.40 [1.15]; $P = 0.006$) (**Figure 1**). None of the patients experienced hypoglycemia.

LABORATORY PROFILES

There were no significant differences in any of the lipid concentrations between baseline and posttreatment (total cholesterol [TC], 176.00 [64.27] vs

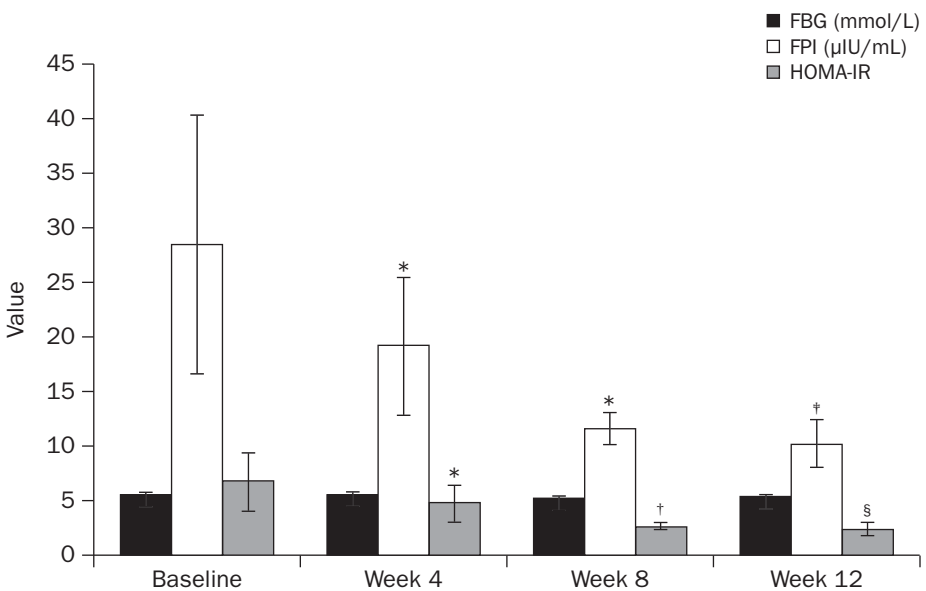

Figure 1. Fasting blood glucose (FBG) concentration, fasting plasma insulin (FPI) concentration, and Homeostasis Model Assessment Index of Insulin Resistance (HOMA-IR) scores at baseline and after receiving rosiglitazone for 4, 8, and 12 weeks. HOMA-IR (mmol/L × μIU/mL) = fasting glucose (mmol/L) × fasting insulin (μIU/mL)/22.5. Analyzed using the Friedman test. *P = 0.005 versus baseline; †P = 0.011 versus baseline; ‡P = 0.01 versus baseline; §P = 0.006 versus baseline.

186.09 [56.02] mg/dL; LDL-C, 97.08 [27.25] vs 104.91 [32.17] mg/dL; triglyceride [TG], 215.36 [259.30] vs 198.33 [242.29] mg/dL; and HDL-C, 48.92 [17.87] vs 45.36 [19.11] mg/dL, respectively) (**Table**). The mean FBG concentration at baseline was 5.45 (0.59) mmol/L (range, 4.27–6.00 mmol/L).

No significant differences were found in blood pressure or liver enzyme activities in these patients at baseline compared with week 12. There were also no significant changes in mean (SD) weight (61.12 [6.30] vs 62.57 [6.06] kg) or BMI (22.97 [1.72] vs 23.23 [1.53] kg/m^2) between baseline and posttreatment, respectively. However, 7 of the 12 patients (58.3%) showed an increase in weight after taking rosiglitazone for 4 weeks. Patients' weight slowly decreased after taking rosiglitazone for 8 and 12 weeks. Mean weight increase compared with baseline was 16.57 [37.47] kg after week 4, 3.82 [1.57] kg after week 8, and 4.30 [2.68] kg after week 12.

BODY COMPOSITION

After week 4 of treatment, 5 patients (41.7%) were found to have peripheral edema—3 had moderate edema and 2 had mild edema. The edema decreased over time; after

Table. Laboratory profile of Thai patients without diabetes mellitus undergoing continuous ambulatory peritoneal dialysis at baseline and after 12 weeks of rosiglitazone treatment (N = 12).

Parameter	Baseline	Week 12	Δ	*P**
Weight, kg				
Mean (SD)	61.12 (6.30)	62.57 (6.06)	1.13 (1.97)	0.176
Range	49.14–80.23	48.23–78.45		
BMI, kg/m^2				
Mean (SD)	22.97 (1.72)	23.23 (1.53)	0.43 (0.85)	0.128
Range	19.24–26.55	18.89–26.73		
SBP, mm Hg				
Mean (SD)	141.42 (19.58)	128.91 (30.26)	–14.18 (27.48)	0.099
Range	120–180	90–201		
DBP, mm Hg				
Mean (SD)	84.67 (13.92)	82.18 (14.52)	–2.27 (13.85)	0.541
Range	60–113	70–108		
TC, mg/dL				
Mean (SD)	176.00 (64.27)	186.09 (56.02)	10.18 (36.25)	0.423
Range	100–349	87–318		
TG, mg/dL				
Mean (SD)	215.36 (259.30)	198.33 (242.29)	–22.18 (78.34)	0.534
Range	57–934	44–916		
HDL-C, mg/dL				
Mean (SD)	48.92 (17.87)	45.36 (19.11)	–1.82 (17.98)	0.959
Range	34–82	24–86		
LDL-C, mg/dL				
Mean (SD)	97.08 (27.25)	104.91 (32.17)	7.27 (29.41)	0.386
Range	53–130	54–138		
AST, IU/L				
Mean (SD)	29.42 (24.05)	28.80 (16.86)	–3.00 (22.85)	0.917
Range	14–96	14–61		
ALT, IU/L				
Mean (SD)	23.42 (18.25)	24.50 (12.25)	0.80 (14.73)	0.779
Range	4–65	11–56		

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; TG = triglyceride; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
*Wilcoxon signed rank test.

week 8, a total of 4 patients (33.3%) were found to have edema—2 had moderate edema and 2 had mild edema. After 12 weeks of rosiglitazone administration, 2 patients (16.7%) had mild edema.

Figure 2 shows the mean (SD) body composition of the patients at baseline and after 4, 8, and 12 weeks of rosiglitazone treatment. The Friedman test indicated a significant increase between baseline and posttreatment in total body water (38.03 [4.55] vs 42.44 [5.99] L; $P = 0.018$), extracellular fluid (20.24 [3.75] vs 26.22 [8.69] L; $P = 0.005$), plasma fluid (4.29 [0.80] vs 5.20 [0.93] L; $P = 0.005$), and interstitial fluid (14.99 [2.78] vs 17.68 [3.07] L; $P = 0.040$).

We further investigated the body composition of the 7 patients who experienced weight gain after 4 weeks of treatment. At compared with baseline, week 4, these patients were found to have a significant increase in both total body water (39.07 [4.47] vs 45.58 [13.27] L; $P = 0.018$) and extracellular fluid (21.29 [4.39] vs 24.28 [4.96] L; $P = 0.018$). For the same time period, the statistically significant increases in plasma fluid (4.50 [0.93] vs 5.14 [1.05] L; $P = 0.018$) and interstitial fluid (15.77 [3.26] vs 17.98 [3.67] L; $P = 0.018$) were related to an increase in extracellular fluid.

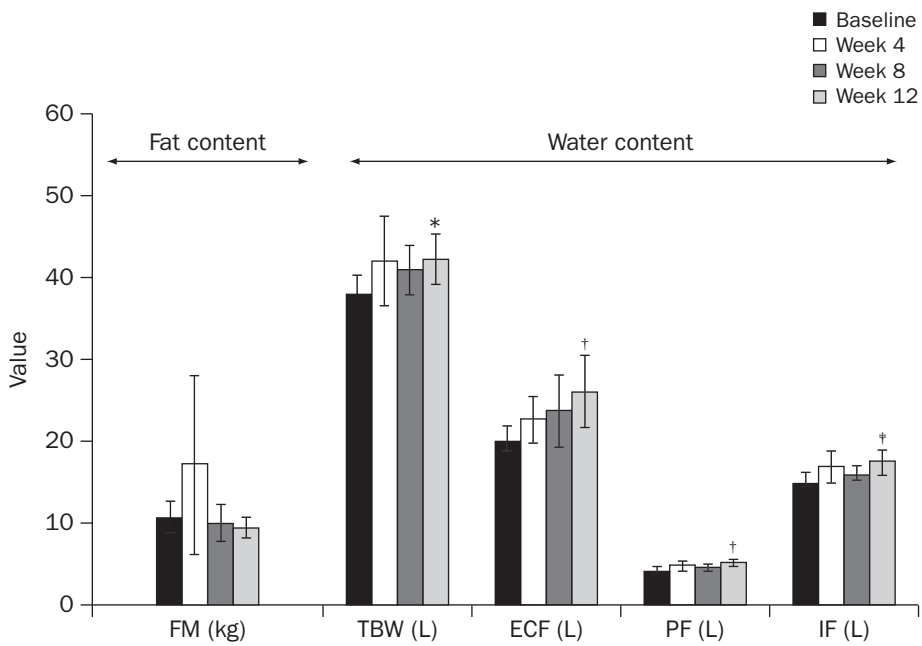

Figure 2. Body composition (fat mass [FM], total body water [TBW], extracellular fluid [ECF], plasma fluid [PF], and interstitial fluid [IF]) at baseline and after 4, 8, and 12 weeks of rosiglitazone treatment using bioelectrical impedance analysis. Analyzed using the Friedman test. *$P = 0.018$ versus baseline; †$P = 0.005$ versus baseline; ‡$P = 0.040$ versus baseline.

TOLERABILITY

No hypoglycemic episodes were observed. No elevation of serum transaminase activities was found after 12 weeks of treatment. There was no significant difference in aspartate aminotransferase (29.42 [24.05] vs 28.80 [16.86] IU/L) or alanine aminotransferase levels (23.42 [18.25] vs 24.50 [12.25] IU/L) between baseline and posttreatment.

DISCUSSION

In this study, nondiabetic uremic patients receiving CAPD therapy had a significant difference in HOMA-IR score (an index of insulin resistance), total body water, extracellular water, plasma fluid, and interstitial fluid between baseline and posttreatment of rosiglitazone administration (2 mg BID). After 12 weeks of treatment, significant reductions were also found in other components of insulin resistance syndrome (eg, fasting plasma insulin concentration).

Insulin resistance is associated with arterial wall changes, coronary artery disease, and cardiovascular mortality in patients with chronic kidney diseases.[26,27] The use of rosiglitazone 4 mg/d was associated with significantly lower fasting plasma insulin concentrations and HOMA-IR scores after 12 weeks of treatment without hypoglycemic episodes in these nondiabetic patients, similar to the results reported by Lin et al.[25] The present pilot study found that rosiglitazone administration for 12 weeks was associated with an apparent increase in weight, but not a statistically significant increase in these patients.

No abnormal liver function tests associated with rosiglitazone administration were found in this study. Our findings regarding lipid profiles suggest that TC and LDL-C increased by ~5.8% and ~8.1%, respectively, compared with baseline, while TG and HDL-C decreased by ~8.2% and ~6.9%, respectively, between baseline and 12 weeks of treatment. However, there were no significant differences in any of the lipid concentrations between baseline and posttreatment, and the results were consistent with those reported by other researchers. O'Moore-Sullivan and Prins[28] found that patients treated with rosiglitazone for 16 months experienced an increase of TC and LDL-C concentrations by 15% to 20% during the first few months of therapy but not at a significant level. Yki-Järvinen[29] found that rosiglitazone, after 26 weeks of treatment at a dose of 4 to 8 mg/d, was associated with a significant decrease in TG concentration by 9% from baseline. In addition, the reduction in HDL-C concentration associated with rosiglitazone treatment has been reported in previous studies.[30,31]

Rosiglitazone may increase fat mass by shifting visceral fat to subcutaneous fat.[32] Our study found no significant changes in fat mass after 12 weeks of rosiglitazone therapy. We hypothesized that the mean (SD) weight increase of 4.30 (2.68) kg after 12 weeks of treatment in these 7 patients might have been associated with an elevation of total body water that resulted in peripheral edema of 6.50 (12.16) L; it was not related to fat mass, which decreased by 1.27 (0.74) kg after week 4 of treatment. This suggests that the change in body weight was related to nonfat components (eg, water composition).

These results are not consistent with those of Carey et al,[33] which examined the effect of rosiglitazone (8 mg/d in 2 divided doses for 16 weeks) in a randomized,

double-blind, placebo-controlled study in patients with type 2 DM. They found a significant increase in fat mass, whereas the increase in fat free mass was not significant in patients with type 2 DM receiving rosiglitazone. The differences in the findings of the 2 studies may be due to differences in rosiglitazone dose and treatment duration. Also, the previous study was evaluated in European patients with type 2 DM who had higher body fat content than Asian CAPD patients without DM.[34,35] Thiazolidinediones have been reported to directly stimulate lipogenic genes and increase adipose tissue mass[36,37]; therefore, patients with a high percentage of fat may show a higher degree of activation, resulting in an increase in fat mass.

Because a strong relationship between insulin resistance and chronic kidney diseases among nondiabetic patients has been reported,[38] detection and treatment of insulin resistance should be considered, even in nondiabetic patients with chronic kidney diseases.

LIMITATIONS

A limitation of this study was its design as an observational study using a pretest and posttest with a repeated-measure design. Although our results were statistically significant, this does not imply clinical significance unless a large sample size is used and the study design controls for other confounding factors. Statistical significance may not represent clinical importance or relevance to patient care. Elevation of serum transaminase activities was not found to be statistically significant. This may be due to the duration of the study or the small sample size, which may not have been sufficient to note significant differences in liver function tests or other end points. Furthermore, bias in peripheral edema evaluation might have occurred, since the physicians who performed the physical examinations were aware of the study objectives. Therefore, future study should be carried out in large, double-blind, randomized, controlled trials. The mechanism of peripheral edema after thiazolidinedione use in patients with chronic kidney disease should also be investigated further.

This pilot study investigated only a small number of patients; changes in patient management should not be made based on these preliminary findings alone. For statistical analysis, the α value of 0.05 was used to detect important differences. However, an α level of 0.001 would yield a more sensitive significant difference with a higher degree of detection.

CONCLUSIONS

Administration of rosiglitazone (2 mg BID) for 12 weeks was associated with significantly reduced fasting plasma insulin concentration as well as insulin resistance in this small number of Thai patients without DM undergoing CAPD. Total body water and extracellular water increased significantly from baseline after 12 weeks of rosiglitazone administration; however, after 12 weeks of treatment, mild peripheral edema was found in 2 of these patients (15.4%). During rosiglitazone therapy, no hypoglycemic episodes or abnormal liver function levels were observed.

ACKNOWLEDGMENTS

The authors wish to acknowledge GlaxoSmithKline (Research Triangle Park, North Carolina) for supplying the rosiglitazone maleate. This work was supported by a grant from the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

REFERENCES

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
2. Sarafidis PA, Whaley-Connell A, Sowers JR, Bakris GL. Cardiometabolic syndrome and chronic kidney disease: What is the link? *J Cardiometab Syndr*. 2006;1:58–65.
3. Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med*. 1974;290:697–701.
4. Canbakan M, Sahin GM. Icodextrine and insulin resistance in continuous ambulatory peritoneal dialysis patients. *Ren Fail*. 2007;29:289–293.
5. Wu HY, Hung KY, Huang JW, et al. Initial glucose load predicts technique survival in patients on chronic peritoneal dialysis. *Am J Nephrol*. 2008;28:765–771.
6. Maggs DG, Buchanan TA, Burant CF, et al. Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1998;128:176–185.
7. Schwartz S, Raskin P, Fonseca V, Graveline JF, for the Troglitazone and Exogenous Insulin Study Group. Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J Med*. 1998;338:861–866.
8. Raskin P, Rendell M, Riddle MC, et al, for the Rosiglitazone Clinical Trials Study Group. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care*. 2001;24:1226–1232.
9. Liazos E, Broadbent DM, Beare N, Kumar N. Spontaneous resolution of diabetic macular oedema after discontinuation of thiazolidenediones. *Diabet Med*. 2008;25:860–862.
10. Berlie HD, Kalus JS, Jaber LA. Thiazolidinediones and the risk of edema: A meta-analysis. *Diabetes Res Clin Pract*. 2007;76:279–289.
11. Karalliedde J, Buckingham R, Starkie M, et al, for the Rosiglitazone Fluid Retention Study Group. Effect of various diuretic treatments on rosiglitazone-induced fluid retention. *J Am Soc Nephrol*. 2006;17:3482–3490.
12. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: A consensus statement from the American Heart Association and American Diabetes Association. *Diabetes Care*. 2004;27:256–263.
13. Starner CI, Schafer JA, Heaton AH, Gleason PP. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. *J Manag Care Pharm*. 2008;14:523–531.
14. Hong G, Lockhart A, Davis B, et al. PPARgamma activation enhances cell surface ENaCalpha via up-regulation of SGK1 in human collecting duct cells. *FASEB J*. 2003;17:1966–1968.
15. Rossier BC, Canessa CM, Schild L, Horisberger JD. Epithelial sodium channels. *Curr Opin Nephrol Hypertens*. 1994;3:487–496.

16. Ciaraldi TP, Kolterman OG, Scarlett JA, et al. Role of glucose transport in the postreceptor defect of non-insulin-dependent diabetes mellitus. *Diabetes*. 1982;31:1016–1022.
17. Ciaraldi TP, Kong AP, Chu NV, et al. Regulation of glucose transport and insulin signaling by troglitazone or metformin in adipose tissue of type 2 diabetic subjects. *Diabetes*. 2002;51: 30–36.
18. Kelly IE, Han TS, Walsh K, Lean ME. Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes [published correction appears in *Diabetes Care.* 1999;22:536]. *Diabetes Care.* 1999;22:288–293.
19. Larsen PJ, Jensen PB, Sørensen RV, et al. Differential influences of peroxisome proliferator-activated receptors gamma and -alpha on food intake and energy homeostasis. *Diabetes*. 2003;52:2249–2259.
20. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
21. Keskin M, Kurtoglu S, Kendirci M, et al. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. *Pediatrics*. 2005;115:e500–e503.
22. Ikeda Y, Suehiro T, Nakamura T, et al. Clinical significance of the insulin resistance index as assessed by homeostasis model assessment. *Endocr J*. 2001;48:81–86.
23. Shoji T, Emoto M, Nishizawa Y. HOMA index to assess insulin resistance in renal failure patients. *Nephron*. 2001;89:348–349.
24. Kim MG, Park SY, Ha SH, et al. Objective interpretation of severity of SLS induced edema by stereoimaging. *J Dermatol Sci*. 2004;35:125–131.
25. Lin SH, Lin YF, Kuo SW, et al. Rosiglitazone improves glucose metabolism in nondiabetic uremic patients on CAPD. *Am J Kidney Dis*. 2003;42:774–780.
26. Stenvinkel P, Heimbürger O, Paultre F, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int*. 1999;55:1899–1911.
27. Shoji T, Emoto M, Shinohara K, et al. Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. *J Am Soc Nephrol*. 2001;12:2117–2124.
28. O'Moore-Sullivan TM, Prins JB. Thiazolidinediones and type 2 diabetes: New drugs for an old disease [published correction appears in *Med J Aust.* 2002;177:396]. *Med J Aust*. 2002;176: 381–386.
29. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351:1106–1118.
30. Keidar S, Guttmann H, Stam T, et al. High incidence of reduced plasma HDL cholesterol in diabetic patients treated with rosiglitazone and fibrate. *Pharmacoepidemiol Drug Saf*. 2007; 11:1192–1194.
31. Normén L, Frohlich J, Montaner J, et al. Combination therapy with fenofibrate and rosiglitazone paradoxically lowers serum HDL cholesterol. *Diabetes Care*. 2004;27:2241–2242.
32. Kim SK, Hur KY, Kim HJ, et al. The increase in abdominal subcutaneous fat deposit is an independent factor to determine the glycemic control after rosiglitazone treatment. *Eur J Endocrinol*. 2007;157:167–174.
33. Carey DG, Cowin GJ, Galloway GJ, et al. Effect of rosiglitazone on insulin sensitivity and body composition in type 2 diabetic patients [published correction appears in *Obes Res.* 2002;10: following table of contents]. *Obes Res*. 2002;10:1008–1015.
34. Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. *Am J Med*. 2003;115(Suppl 8A):42S–48S.

35. Mayerson AB, Hundal RS, Dufour S, et al. The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes*. 2002;51:797–802.
36. Mori Y, Murakawa Y, Okada K, et al. Effect of troglitazone on body fat distribution in type 2 diabetic patients. *Diabetes Care*. 1999;22:908–912.
37. Okuno A, Tamemoto H, Tobe K, et al. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J Clin Invest*. 1998; 101:1354–1361.
38. Chen J, Muntner P, Hamm LL, et al. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. *J Am Soc Nephrol*. 2003;14:469–477.

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